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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,782	12/10/2003	Stephen Hsu	275.0007 0101	6883

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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/732,782	HSU ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,17,25,26 and 33* is/are pending in the application.

4a) Of the above claim(s) *1,7-9 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6,10,11,17,25,26 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Claims 1-12, 17, 25, 26 and 33 are pending, and claims 1, 7-9, and 12 have been withdrawn from consideration as being drawn to a non-elected invention.

2. Claims 2-6, 10, 11, 17, 25, 26, and 33 are under examination.

3. Applicant's election with traverse of the invention of Group IV and of the species "detecting p57/KIP protein", "an oral cancer", and "primary epidermal keratinocytes" in the reply filed on August 4, 2006 is acknowledged. The traversal is on the ground(s) that the methods of Groups I-V all involve overlapping method steps and that the claims are so interrelated that a search for one group of claims will reveal art relevant to the other groups. This argument is not found persuasive because the searches for each of Groups I-V, while overlapping with the searches for the other cited groups, would not be coextensive. Thus, searching any of Groups I-V together would pose an undue search burden. The requirement for restriction is proper and is made FINAL.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2-6, 10, 11, 17, 25, 26, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-6, 10, 11, 17, 25, 26, and 33 are objected to in that the term "a higher p57/KIP2 level" in claim 10 is a relative term which renders the claims indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 2-6, 10, 11, 17, 25, 26, and 33 are objected to as being indefinite in the use of the term p57/KIP2 as the sole means of identifying the claimed protein. The use of laboratory designations only to identify a particular protein renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct proteins. Amendment of the claims to unambiguously define the claimed protein is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-6, 10, 11, 17, 25, 26, and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims, as drawn to the elected invention, are as follows:

A method of determining the therapeutic effectiveness of an agent, the method comprising:

contacting normal cells with the agent;

determining the p57/KIP2 level in the normal cells after contacting with the agent;

contacting cancer cells with the agent;

determining the p57/KIP2 level in the cancer cells after contacting with the agent; and

comparing the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2 level in the cancer cells after contacting with the agent;

wherein a higher p57/KIP2 level in the normal cells compared to the p57/KIP2 level in the cancer cells indicates that agent is effective for the treatment of cancer (claim 10),

Wherein the cancer cell is an epithelial carcinoma cell line (claim 2),

Wherein the cancer cell is an epithelial carcinoma cell line, wherein the epithelial carcinoma cell line is selected from the group consisting of an oral squamous carcinoma cell line and a metastatic oral carcinoma cell line (claim 3),

Wherein the cancer cells are derived from a human epithelial carcinoma (claim 4),

Wherein the cancer cells are derived from a human epithelial carcinoma, wherein the human epithelial carcinoma is selected from the group consisting of an oral squamous carcinoma and a metastatic oral carcinoma (claim 5),

Wherein determining the p57/KIP2 level is by detecting the p57/KIP2 protein (claim 6);

Wherein the normal cells and cancer cells are cultured together (claim 11);

Wherein the cancer cells are oral cancer (claim 17);

Wherein both the cancer cells and normal cells are of epithelial origin (claim 25);

Wherein both the cancer cells and normal cells are human cells (claim 26);

Wherein the normal cells are normal human primary epidermal keratinocytes (claim 33).

The specification teaches that a number of studies have shown that polyphenolic compounds such as those found in green tea possess a chemopreventive and apoptotic activity against certain cancers (page 15, lines 9-12). The specification teaches that a western blot analysis to examine the effects of green tea polyphenols on expression levels of p57 (KIP2) (a cyclin dependent kinase and apoptosis inhibitor) in normal human keratinocytes and in the oral carcinoma cell lines SCC25 and OSC2 showed that the most potent green tea polyphenol, (-)-epigallocatechin-3-gallate (EGCG), induced p57 in normal keratinocytes while levels of P57 protein in oral carcinoma cells were unaltered (Example 1). The specification also teaches that the differential response in p57 induction was consistent with the apoptosis status detected by annexin V assay (Example 1). The specification also teaches that green tea polyphenols activate two pathways, with one being survival through p57 induction and a second being caspase 3-dependent apoptosis without p57 induction, and that the p57 induction by green tea polyphenols in normal epithelial cells serves as an anti-apoptotic function (Example 2). The specification further teaches that, in cells that lack p57 induction, green tea polyphenols induced Apaf-1 expression along with caspase 3 activation leading to apoptotis, whereas cells with poly-phenol-inducible p57 maintained constant levels of Apaf-1 and proliferating nuclear antigen (PCNA) with basal caspase 3 activity, and that

retroviral-transfected, p57-expressing oral carcinoma cells showed significant resistance to green tea polyphenol-induced apoptosis (Example 3). The specification also teaches that an examination of whether wild type caspase 3 is required for GTPPs-induced apoptosis showed that the caspase 3 null MCF7 cell line did not exhibit any morphological alterations in response to treatment with GTPPs whereas MCF7 cells transfected to express caspase 3 were eliminated by treatment with GTPPs (Example 4). The specification also teaches that EGCG induced differentiation and proliferation, and is associated with p57/KIP2 induction, in epidermal keratinocytes as measured by the expression of keratin 1, filaggrin and transglutaminase activity (Example 5). The specification also teaches that an examination of the oxidative status of normal epithelial, normal salivary glandular cells and oral carcinoma cell lines treated with EGCG using reactive oxygen species (ROS) measurement and catalase and superoxide dismutase (SOD) activity assays demonstrated that high concentrations of EGCG induced oxidative stress only in tumor cells (Example 6). The specification also teaches a system that is able to screen potential chemopreventative or therapeutic agents wherein tumor cell death and normal cell survival are detected simultaneously in a device that co-cultures normal human cells adjacent to human tumor cells (Example 7).

The teaching of the specification cannot be extrapolated to enable the claims because one of skill in the art could not predict that the invention would function as claimed in determining the therapeutic effectiveness of an agent wherein a higher level of p57/KIP2 in the normal cells contacted with the agent compared to the p57/KIP2 level in the cancer cells contacted with the agent indicates the agent is effective for the treatment of cancer. In a first aspect, one cannot extrapolate the teaching of the specification to the enablement of the claims because the finding that green tea polyphenols induce a p57/KIP2 response in normal cells but not in cancer cell lines, is not sufficient to establish that such a differential effect occurs in vivo. Differences between cells in culture and primary cells in vivo are well known in the art. In particular, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc.,

1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, an anti-cancer agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action, at a sufficient concentration, and for a sufficient period of time. In addition, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In vitro assays cannot duplicate the complex conditions of in vivo therapy. In the assays, the anti-tumor agent is in contact with cells during the entire exposure period. This is not the case in vivo, where exposure at the target site may be delayed or inadequate. Variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The agent may be inactivated in vivo before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or

due to an inherently short half-life of the agent and the in vitro tests of record do not sufficiently duplicate the conditions that occur in vivo. In addition, the agent may not otherwise reach the target because of an inability to penetrate tissues or cells where activity is to be exerted, or because it may be absorbed by fluids, cells and tissues where the agent has no effect, because circulation into the target area may be insufficient to carry the agent and a large enough local concentration may not be established. Thus, based on cell culture data it could not be predicted that the differential effects observed in vitro would be found in the *in vivo* environment and that the invention would function as claimed in determining the therapeutic effectiveness of an agent in the treatment of cancer.

Further, one cannot extrapolate the teaching of the specification to the enablement of the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. For example, Gura (1997, Science 278:1041-1042) teaches that researchers face the problem of sifting through potential anti-cancer agents to find ones promising enough to make human clinical trials worthwhile and teaches that, since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para.). Thus, if anti-cancer agents that have success in inhibiting the growth of cancer cells in vitro cannot be predicted to have potential therapeutic success, it certainly cannot be predicted that agents for which no such activity has been demonstrated will be successful in the treatment of cancer. Further, in the instant case, the specification does not provide any working examples (i.e. any in vitro or in vivo evidence) that agents induce a higher level of p57/KIP2 in normal cells versus cancer cells are effective for the treatment of cancer other than green tea polyphenols, which agents, as set forth above, were shown to have two activities: (i) survival activation through p57 induction and (ii) caspase 3-dependent apoptosis inducing activity. Clearly, as taught in the specification, identifying compounds that initiate survival activation through p57 induction, without further identifying the compounds as having apoptosis inducing activity in the absence

of p57 induction will not allow one of skill in the art to predict that the identified compounds will be effective for the treatment of cancer.

Thus, given the unpredictability of the cancer therapeutic arts and the lack of any working examples in the specification that show that agents identified via the claimed methods will be effective for the treatment of cancer, it cannot be predicted that the invention will function as claimed. Thus, undue experimentation will be required to practice the invention.

8. No claims are allowed.

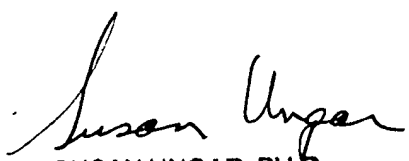
9. All other objections and rejections set for the in the previous Office Action are withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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